IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Timothy O'Brien et al.	Group Art Unit: 1642
Serial No.:	10/715,066	Examiner: Peter J. Reddig
Filed:	October 17, 2003	Docket No.: 110.018US3
Title:	CA125 GENE AND ITS USE FOR DIAGNOSTIC AND THERAPEUTIC INTERVENTIONS	

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We, Timothy O'Brien, John Beard, and Lowell Underwood, declare and say as follows:

1. We are co-inventors of the subject matter claimed in the above-identified U.S. Patent Application.

2. We have reviewed the Office Action mailed August 8, 2008, in the above-identified patent application. We make this declaration in support of the patentability of the claims of the above-referenced U.S. Patent Application.

3. The Examiner stated in the Office Action that Algate et al. (WO 2001/51513), published July 19, 2001 and filed January 16, 2001, discloses a nucleic acid that encodes a polypeptide homologous to amino acid residues 21,897 to 22,065 of SEQ ID NO:5 of our above-identified patent application.

4. We conceived and reduced to practice in the United States of America before January 16, 2001, so much of the claimed invention of claim 27 of "An isolated nucleic acid molecule encoding residues 10,432 to 22,152 of SEQ ID NO:5 or a fragment of residues 10,432 to 22,152 of SEQ ID NO:5; wherein the isolated nucleic acid molecule is an expression vector and is adapted to express in a cell residues 10,432 to 22,152 of SEQ ID NO:5 or a fragment of residues 10,432 to 22,152 of SEQ ID NO:5; wherein the fragment of residues 10,432 to 22,152 of SEQ ID NO:5 is an antigenic fragment that can be used to make monoclonal antibodies that specifically recognize CA125" as is alleged by the Examiner to be disclosed by Algate et al. Specifically, we conceived and reduced

to practice a nucleic acid encoding more than residues 21,897 to 22,065 of SEQ ID NO:5 and an expression vector encoding and expressing an antigenic fragment thereof that can be used to make monoclonal antibodies that specifically recognize CA125.

5. Our conception and reduction to practice in the United States of America before January 16, 2001, of a nucleic acid encoding more than residues 21,898 to 22,065 of SEQ ID NO:5 and an expression vector encoding and expressing an antigenic fragment thereof that can be used to make monoclonal antibodies that specifically recognize CA125 is evidenced by Exhibit A and Exhibit B submitted with this Declaration.

6. Exhibit A is an Invention Disclosure Form submitted by Timothy O'Brien to the University of Arkansas before January 16, 2001 (dates redacted). Fig. 5a of the invention disclosure form, on pages 11 and 12 shows a sequence of 12 multiple repeat units and the carboxy terminus of CA125. From residue 1938 to 2105 is identical to residues 21898 to 22065 of SEQ ID NO:5, which is the sequence shown in Appendix 3 of the Office Action as aligning with what is alleged to be a sequence disclosed in Algate. Fig. 5b is the nucleic acid encoding the protein sequence of Fig. 5a of Exhibit A.

7. Exhibit B is a photocopy of several pages of the laboratory notebook of Applicant John Beard. Page 1 of Exhibit B discloses plans to perform a Western blot with antibodies M11 and OC125. Pages 4 and 6 list volumes of reagents for a PCR reaction mixture and a ligation reaction mixture to create an expression vector. Page 6 discloses "inducing" expression of the vector and performing a "Western" blot with "M11/OC125." Page 7 discloses a Western blot with "M11 + OC125 Abs against Recomb. CA125 repeat" and shows strong staining between 33 and 17 kDa, just as is shown in Fig. 5B of parent patent application PCT/US02/11734. All the pages in Exhibit B are dated before January 16, 2001 (dates redacted).

8. Exhibits A and B demonstrate that we were in possession of and had reduced to practice in the United States before January 16, 2001, recombinant nucleic acids encoding residues 21898 to 22065 of SEQ ID NO:5 and surrounding sequences; and we were in possession of and had reduced to practice in the United States before January 16, 2001, an expression vector that expressed a recombinant fragment of CA125 that was

recognized by a monoclonal antibody (M11) that recognizes CA125 and therefore could by used to make monoclonal antibodies that specifically recognize CA125.

9. All statements made herein of our own knowledge are true, and all statements made on information and belief are believed to be true. Furthermore, these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and with knowledge that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 12/01/08 By: _____
Timothy O'Brien

Dated: 12/1/08 By: _____
John Beard

Dated: 12/01/08 By: _____
Lowell Underwood

Exh. 64 A

I01-07

Date Rec'd BBC [redacted]/agn

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CONFIDENTIAL

UNIVERSITY OF ARKANSAS
INVENTION DISCLOSURE FORM

A. Descriptive

1. Name(s), title(s), and University address(es), telephone number(s) for inventor(s):

Name: **Timothy J. O'Brien, Ph.D.** Name:

Title: **Professor, Obstetrics & Gynecology** Title:

Address: Address:
4301 West Markham, Slot 718
Little Rock, AR 72205

Phone: **(501) 686-6696** Phone:

Use additional sheets if necessary.

2. Title of Invention:
CA125; Cloning of Epitope Repeats and Carboxy terminus of Gene

3. Description of the invention. Please provide significant detail in a summary roughly between 75 and 150 words.

Consider the following in your description: Is the invention a new process, composition of matter, a device, or one or more products? Is it a new use for, or an improvement to, an existing product or process? Is the invention a work of authorship (including computer software)?

Here we describe the cloning of the repeat sequences of the CA125 gene. CA125 has been used for more than 15 years to monitor patients with ovarian cancer for response to therapy and detection of recurrent disease. The CA125 molecule is defined by specific antibodies developed in the 1980's and while the glycoprotein has been described biochemically and metabolically by ourselves and others (see attachment), no one has yet

6. Does the invention possess disadvantages or limitations? How can they be overcome?

The current limitations are that we have not yet completed sequencing the amino terminal end of the molecule which will provide further insight into its clinical applications. However, the repeat domains are the business part of the molecule currently utilized in testing and therapy.

7. Provide an sketches, drawings, photographs, manuscripts, and other materials that help illustrate the description. (Rough artwork, flow sheets, Polaroid photographs and penciled graphs are satisfactory).

See attached figures.

8. Disclosure Information

(a) Earliest date and place invention was conceived (Identify persons and records to support date and place):

Sequence data from cyanogen bromide fragments obtained in 1996 - 1997. PCR data for normal versus tumor and repeat sequence obtained in [redacted]. Data are recorded in lab manuals in Barton Research, room 5R/11, John Beard, chief technician.

(b) Date and present location of first sketch, drawing or photo and first written description (Such as, notebook entries, etc.):

Barton Research, 5R/11.

(c) Is a prototype available that demonstrates the use(s) of the invention? Provide date, place of completion of first prototype, and its present location.

N/A

(d) Date and place of first test or operation and the results (Give name and address of witnesses, and present location of records):

Barton Research, 5R/11.

(e) Has the invention ever been disclosed or described in written form? If so please provide a copy.

No.

(f) Has the invention ever been disclosed in an oral presentation? If so, please provide date and name of meeting.
No.

(g) Has the invention been tested? State circumstances and dates.

No.

(h) Has the invention ever been used experimentally? State time and place.

No.

(i) Has the invention been used routinely? Explain circumstances.

No.

B. Other Pertinent Data

1. Are there publications such as theses, reports, and reprints pertaining to the invention?

   Please list references and attach copies insofar as possible. Include manuscripts for publication (submitted or not), new releases, featured articles, and items for internal news releases, featured articles, and items for internal publications.

   No.

2. Are laboratory records and data available? Give reference numbers and physical location but do not enclose.

   Yes, Barton Research, Room 5R/11, John Beard.

3. Are related patents or other publications known to the inventor? Please list.

   No.

4. Was the work that led to the invention sponsored? If yes, attach copy of contract or agreement if possible and fill in the proper blanks below.

   No.

   a. Title of government agency _____

   Campus Account No._____

   b. Name of industrial sponsor _____

   c. Name of university sponsor _____

   d. Other sponsor(s) _____

5. Has there been commercial interest? Name companies and specific contacts.

Multiple companies in diagnostics and therapeutics.

6. List other firms that work in the field or may have an interest in the invention.

None known.

7. Signature(s) of inventor(s) and date:

a. _____ (date) [redacted]

b. _____ (date) _____

c. _____ (date) _____

d. _____ (date) _____

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Signature of Department Chair:

_____ (date) [redacted]

Signature of Biotechnology Center:

_____ (date) [redacted]

Exhibit B

Digest.

30µl Cav PCR Prod
3.5µl Buff B
1.0µl BamH I
1.0µl Hind III

O/N @ 37°C

[redacted]

TNT Transc/Transl.

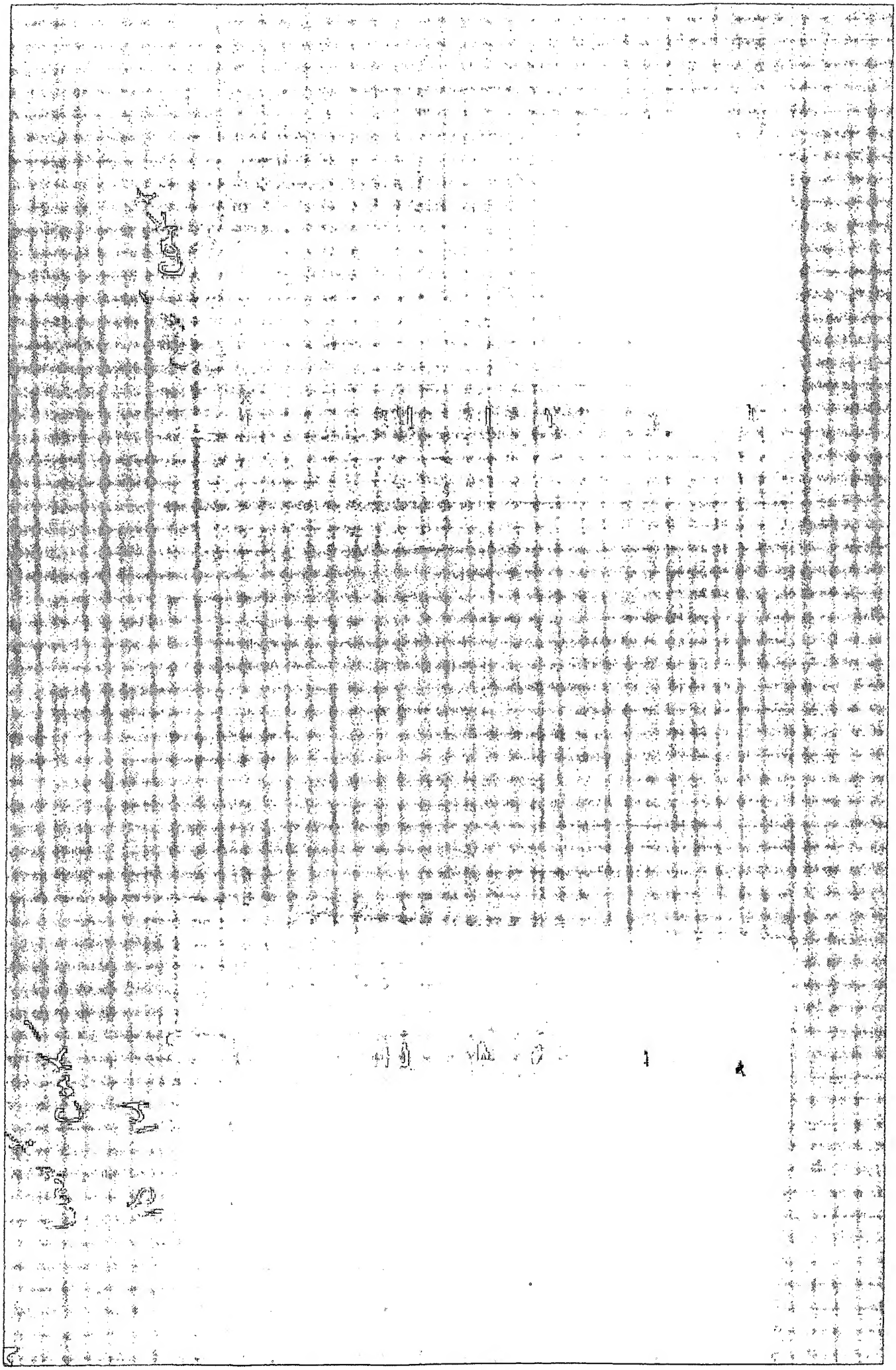
use 9µl of HCav T-10 or HCav T-14
in 50µl rxns 90 min @ 30°C

40µl master mix
9µl plasmid
µl Met

Load 20µl on gel

| M | 14 | 10 | |

western
w/ M11/OC125
use 10 µg/ml of each.



400bp

Ligation Cax into pQE-30 & 40

	(H)	(D)
1.0 µl	pQE-30	or pQE-40
1.0 µl	Ligase	
5.0 µl	Ligase Buffer.	
3.0 µl	400 bp Cax	
10 µl	@ 16°C	O/N.

Start O/N cultures for
H Cax-1 to 5 + D Cax 1 to 4

[redacted] M.n.s for O/N's

Digest.

		12x
10.8 µl	plasmid	
.3	BamHI	3.6
.3	HindIII	3.6
1.2	10x B~~uf~~B	14.4
12		1.8 ea.

@ 37°C hrs.

T12 } Ab's
14 } & cDNAs
15 } to chr.on

[redacted]

PCR.

5.0µl	1:20	HCax T-10
10		10x Buff
10		10x dNTPs
10		25mM $MgCl_2$
5		5pmol/µl HCax-5
5		" " AS
1.0		Promega Taq.
54		dH_2O

Run 56°C 35x

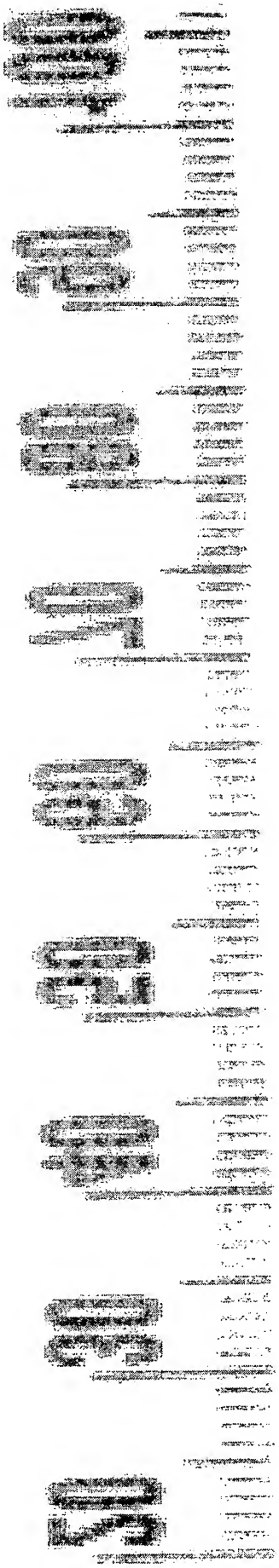
Digests

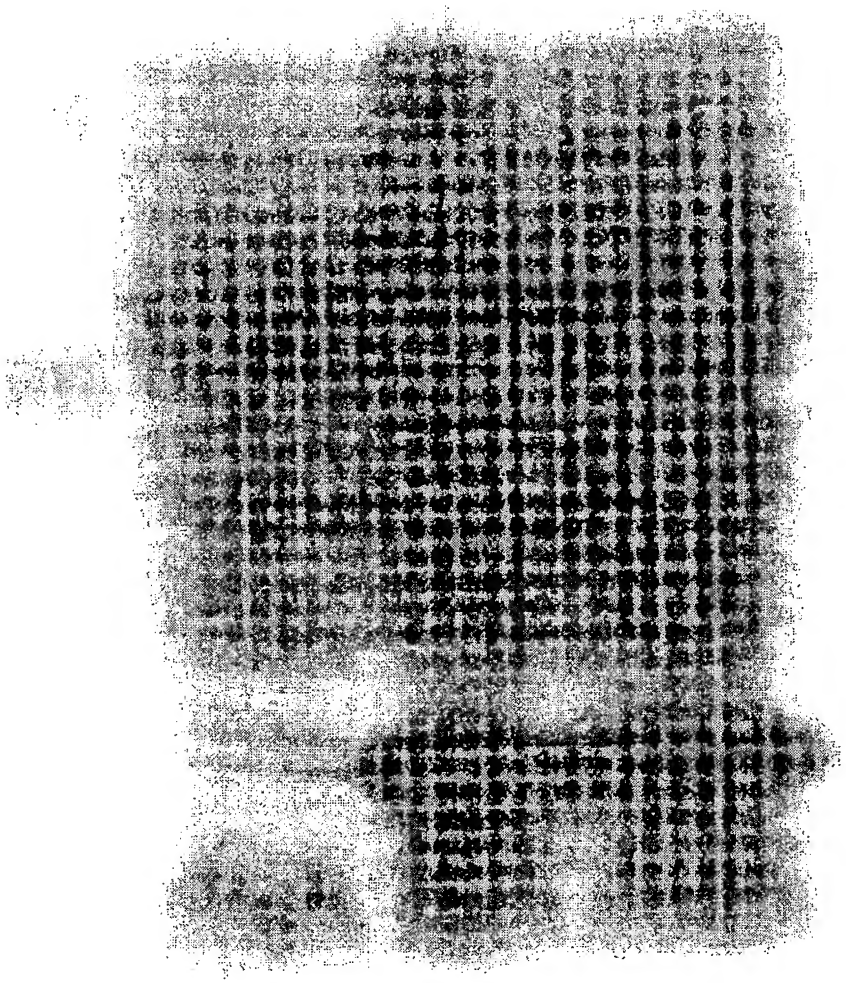
10.2µl	pQE-30, pQE-40 or HCax PCR prod		5x
.3	10x Buff E		1.5
.3	BamHI		1.5
1.2	HindIII		6.0
17			1.5ea

@ 37°C ON

Ligation

1.0µl	T-vector
5.0µl	2x Lig. Buffer
1.0µl	Ligase
3.0µl	HCax PCR prod
10µl	ON @ 16°C





Digest.

pQE-40

10.2 µl	pQE-40 plasmid
.6	Bgl II
.3	Hind III
1.2	Buffer C.
12	@ 37°C O/N.

Ligations

④ Car into pQE-40 BglII BamHI / HindIII
② R.ch 2 ↑ ↑ ↑
③ R.ch 3
① R.ch 1 into pQE-30 HindIII / KpnI

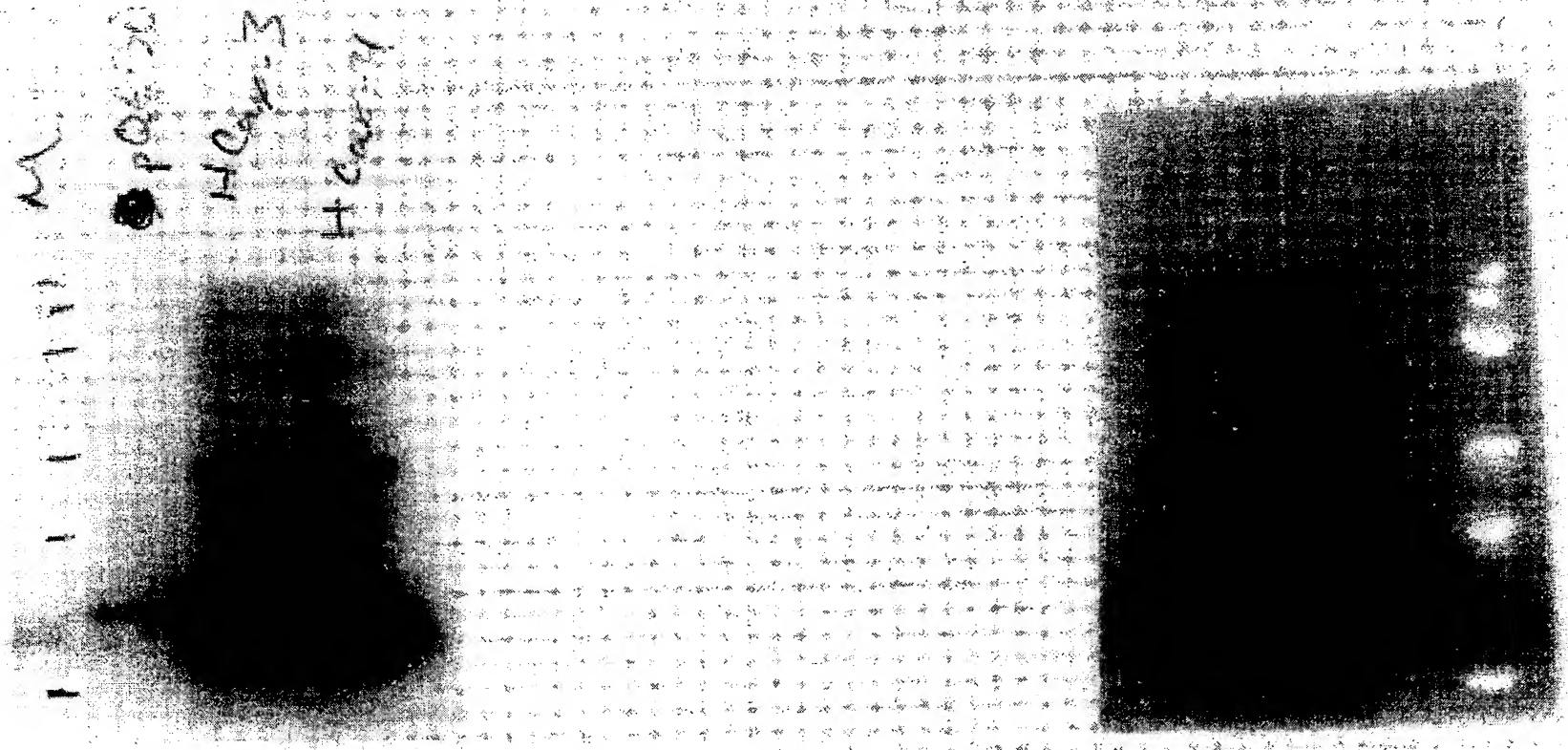
1 µl	vector
1 µl	10x Lig Buffer
1 µl	Ligase
7 µl	insert
10 µl	O/N @ 15°C

[redacted] Induce HCar-3 + HCar-4 or pQE-30 for 5hrs (1mM IPTG)
western & Coomassie.

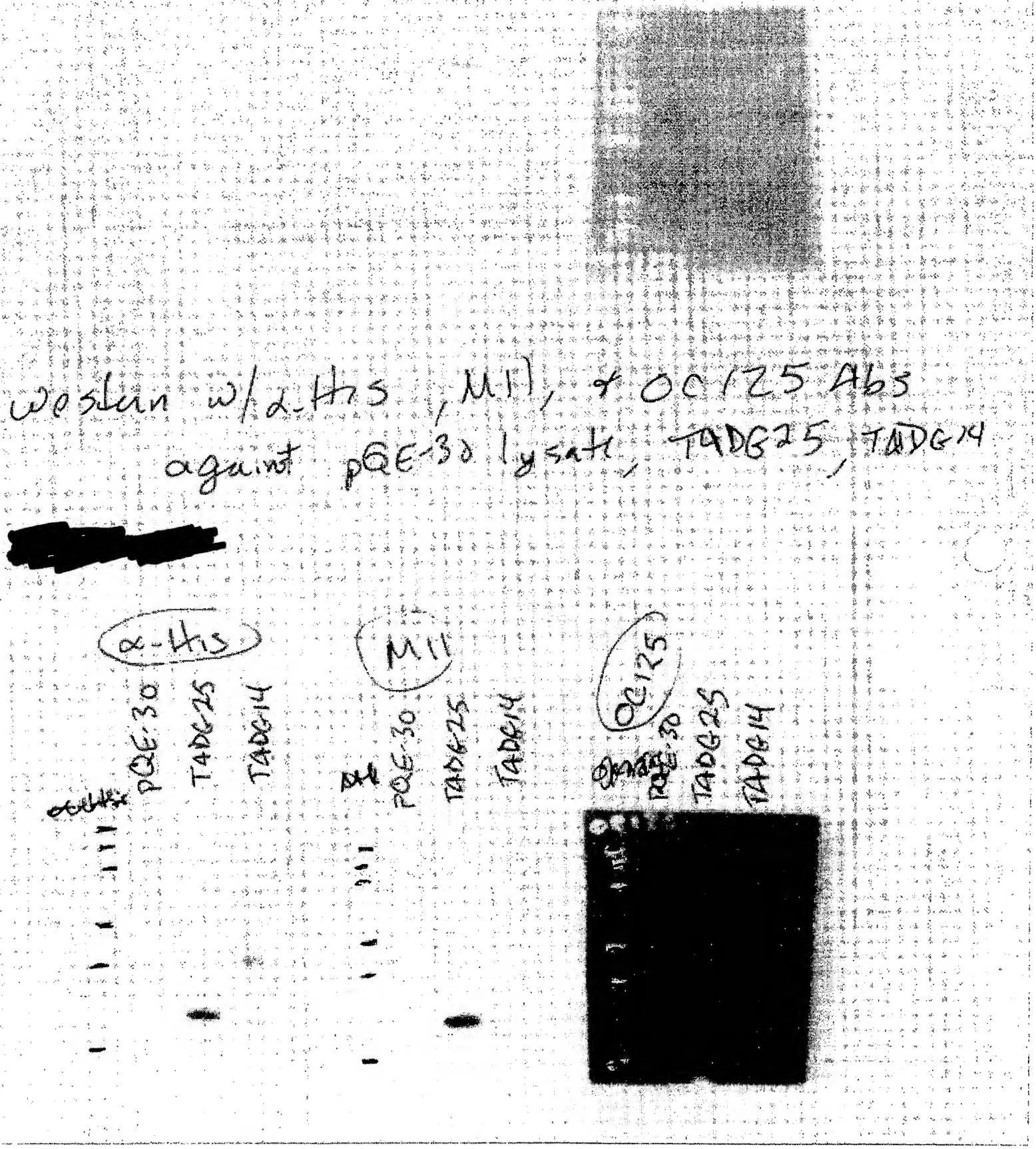
M	3d	3	4

anti/OCI2S western
10 µg/ml

[redacted]



Western
w/ MH toc125-Abs
against Recomb. CA125 Repeat


Western w/ α-His, M11, & OC125 Abs
against pQE-30 lysate, TADG25, TADG14
[redacted]
α-His
pQE-30
TADG25
TADG14
M11
pQE-30
TADG25
TADG14
OC125
pQE-30
TADG25
TADG14